4V

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,665	08/14/2002	Keith Alan Foster	18872.0120	5000

26712 7590 09/08/2005

HODGSON RUSS LLP
ONE M & T PLAZA
SUITE 2000
BUFFALO, NY 14203-2391

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,665	FOSTER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 8-9, 22-28, 31-36, 38, and 40-45* is/are pending in the application.

4a) Of the above claim(s) *31-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 8-9, 22-28, 38 and 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3, 8-9, 22-28, 31-36, 38, and 40-45 are pending.

2. Claims 31-36 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 6/15/05, the following objection and rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3, 8-9, 22-28, 38 and 40-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of inhibiting secretion from a non-neuronal inflammatory cell comprising administering a polypeptide comprising a first domain and a second domain wherein the first domain is a light chain of botulinum neurotoxin containing endopeptidase activity specific for a protein selected from the group consisting of SNAP-25, synaptobrevin and syntaxin covalently linked to a second domain wherein the second domain is a clostrial toxin heavy chain H_N that that translocates the first domain into the cytoplasm of a non-neuronal inflammatory cell thereby inhibits secretion from said cell, (2) the said method wherein the polypeptide further comprises a third domain wherein the third domain is a ligand capable of binding to the surface of non-neuronal inflammatory cells, (3) a polypeptide comprising a first domain, a second domain and a third domain wherein the first domain is a light chain of botulinum neurotoxin containing endopeptidase activity specific for a protein selected from the group consisting of SNAP-25, synaptobrevin and syntaxin covalently linked to a second domain wherein the second domain is a clostrial toxin heavy chain H_N that that translocates the first domain into the cytoplasm of a non-neuronal inflammatory cell and covalently linked to a third domain wherein the domain is a ligand capable of binding to the surface of non-neuronal inflammatory cell and (4) a composition comprising the a polypeptide comprising a first domain, a second domain and a third domain wherein the first domain is a light chain of botulinum neurotoxin containing endopeptidase activity specific for a protein selected from the group

consisting of SNAP-25, synaptobrevin and syntaxin covalently linked to a second domain wherein the second domain is a clostrial toxin heavy chain H_N that that translocates the first domain into the cytoplasm of a non-neuronal inflammatory cell and covalently linked to a third domain wherein the domain is a ligand capable of binding to the surface of non-neuronal inflammatory cell and a pharmaceutical acceptable carrier, **does not** reasonably provide enablement for a method of inhibiting secretion from any non-neuronal inflammatory cell as set forth in claims 1-3, 8-9, 22-28, 38 and 40-45 using (1) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves any one or more proteins essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (2) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves any one or more proteins essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell or for treating any disease, any disease such as the ones recited in claim 9, (3) *any* "agent comprising at least any first and second domains" further comprises any third domain for targeting the agent to said non-neuronal inflammatory cell for the claimed method, (4) a*ny* "agent comprising at least any first and second domains" further comprises any third domain wherein the third domain is IL-8 for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (5) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (6) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell wherein the first domain comprises any light chain of a clostridial neurotoxin, any fragment of any light chain of a clostridial neurotoxin, any variant or derivative of any light chain of a clostridial neurotoxin, (7) any "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell wherein the second domain

comprises any H_N region of a clostridial polypeptide, any fragment of any H_N region of a clostridial polypeptide, any variant or any derivative of any H_N region of a clostridial polypeptide that translocates the exocytosis inhibiting activity of the first domain into the inflammatory cell for the claimed method, (8) any agent comprising at least any first, second and third domains, wherein the first domain cleaves any one or more proteins essential to exocytosis, any second domain translocates the first domain into the cell and the third domain that binds to any non-neuronal inflammatory cell, (9) any pharmaceutical composition comprising any agent comprising at least any first, second and third domains, wherein the first domain cleaves any one or more proteins essential to exocytosis, any second domain translocates the first domain into the cell and the third domain that binds to any non-neuronal inflammatory cell in combination with a pharmaceutical acceptable carrier and (10) a method of treating any disease caused, exacerbated or maintained by secretion from any non-neuronal inflammatory cell using any of the agent mentioned above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a polypeptide comprising a first domain, a second domain and a third domain wherein the first domain is a light chain of botulinum neurotoxin containing endopeptidase activity specific for a protein selected from the group consisting of SNAP-25, synaptobrevin and syntaxin covalently linked to a second domain wherein the second domain is a clostrial toxin heavy chain H_N that that translocates the first domain into the cytoplasm of a non-neuronal inflammatory cell and covalently linked to a third domain wherein the domain is wheat germ agglutinin capable of binding to the surface of non-neuronal inflammatory cell. The specification further discloses a method of inhibiting secretion of

histamine from human umbilical vein endothelial cells in vitro stimulated with von Willebrands factor using the polypeptide mentioned above in the presence low pH (page 42).

The specification does not teach how to make any or all "agent" mentioned above because there is insufficient guidance as to the structure of the "agent" without the amino acid sequence, much less using the undisclosed agent for treating *all* disease such as the ones recited in claims 9 and 38.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages). A person of skill in the art could not predict which particular "agents" without the amino acid sequences are essential and could be used in a therapeutic methods encompassed by the claims.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the unlimited number of "agent" and disease, there is a lack of in vivo working example demonstrating that any "agent" is effective for inhibiting secretion from all non-neuronal inflammatory cell, under physiological condition. Let alone treating all disease such as the ones recited in claim 9, including allergies, eosinophilia, asthma, autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, pancreatitis, radiation induced fibrosis, psoriasis, eczema, and other fibrotic disorders.

A method of treating all disease using any agent mentioned above in the absence of in vivo working example is unpredictable for the following reasons: (1) the agent or protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the agent or protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments and the declarations of Keith Foster and John Chaddock filed 6/15/05 have been fully considered but are not found persuasive.

Applicants' position is that prior to the present invention, it would have been routine for a skilled person to generally prepare agents having first, second, and third domains. The general methodologies are exemplified in specific embodiments of the present application. Additional objective evidence is provided by the enclosed Rule 1.132 Declarations by John Chaddock and Keith Foster in another application 09/529,130. The declaration describe a range of different chemical coupling agents that may be used to link one or more domains of an agent according to the present invention. The efficacy of the claimed agent stems from delivery of the first "endopeptidase" domain into a desired target cell. By way of example, Pinteren et al, 2000 cited in the specification on page 14 describe inhibition of secretion from permeabilized eosinphils presence of botulinum C1 holotoxin (see Figure 4, page 390). Thus, Pinxteren confirm that a clostridial neurotoxin L-chain, once delivered to a target cell (e.g. en eosinophil), has efficacy for treating a condition associated with excessive secretion. Targeting of an agent to a desired cell-type is routinely achieved by linking to a TM that binds to the specific cell type. In this regard, Specht et al (abstract NO 138 on page R43) describes the use of IgE as a TM for targeting mast cells. Following delivery to a desired target non-neuronal inflammatory cell by an appropriate TM, the agents of the present invention exert their effect by cleaving one or more exocytic proteins located in that cell. In this regard, Guo et al confirms that the exocytotic proteins substrates on which the present claimed agents act, such as SNARE proteins including SNAP25, synaptobrevin/VAMP and syntaxin are found in inflammatory cells such as mast cells. Thus, these publications confirm that the presently claimed agents are suitable for treating the recited

conditions (claims 9 and 45) because they can be targeted to non-neuronal inflammatory cells (e.g. mast cells).

In contrast to applicants' assertion that it would have been routine for a skilled person to generally prepare agents having first, second, and third domains, it is NOT routine to make any agent comprising any first domain, second domain and/or third domain without knowing the structure of the first, second and third domain, let alone using the undisclosed agent for a method of inhibiting secretion by non-neuronal inflammatory cell or treating any diseases such as the ones recited in claim 9 and 45. Claims 1 and 22 do not recite the specific agent comprising the specific first domain, and the specific second domain. Claim 23 does not recite the particular "fragment", "variant" or "derivative" of the light chain of clostridial neurotoxin. Claim 38 recites a method of treating any disease caused, exacerbated or maintained by secretion from any non-neuronal cell by administering to any patient any polypeptide that cleaves any one or more proteins essential to exocytosis. None of the claims recite the specific agent that targets to the specific cell type such as eosinophils or mast cells as argued for treating any diseases by way of cleaving exocytotic proteins to inhibit secretion using botulinum C1 holotoxin.

It is noted that the declarations by Keith Foster and John Chaddock are related to application 09/529,130 and are irrelevant to instant application, which is 10/088,665. The agent in application 09/529,130 is an agent for treating pain and irrelevant to the agent and method of inhibiting secretion of a non-neuronal inflammatory cell for treating allergy, or any recited autoimmune disorder such as rheumatoid arthritis, SLE, lung scarring or any other fibrotic disorders. The declaration describe a range of different chemical coupling agents that may be used to link one or more domains of an agent according to the present invention. However, this is not what is being claimed.

In response to applicants' argument that Pinxteren confirm that a clostridial neurotoxin L-chain, once delivered to a target cell (e.g. en eosinophil), has efficacy for treating a condition associated with excessive secretion, Pinxteren et al teach further work is required to identify downstream effectors activated by these GTP-binding proteins and to show how they interact with the SNAP and SNARE isoforms known to present in cells such as eosinophils (see abstract, in particular). In fact, Pinxteren teaches botulinum toxin bontA and BontB have no effect on inhibiting eosinophils secretion (see Figure 1A, in particular).

In response to applicants' argument that Specht et al (abstract NO 138 on page R43) describes the use of IgE as a TM for targeting mast cells, it is noted that none of the claims recite

the particular targeting agent to the particular inflammatory cell such as mast cells. None of the references Pinxteren, Specht and Guo teach a method treating disorders such as autoimmune rheumatoid arthritis, SLE, pancreatitis, radiation induced fibrosis, psoriasis, eczema, and other fibrotic disorders by inhibiting secretion of inflammatory cells using any agent comprising any first domain, and any second domain or any agent comprising any first, second and third domain. The in vitro guinea pig eosinophils model taught by Pinxteren is not an appropriate model for disorder such as rheumatoid arthritis, SLE, pancreatitis, radiation induced fibrosis, psoriasis, eczema, and other fibrotic disorders. Given the unlimited number of agent and disorders to be treated by the undisclosed agent, there is a lack of in vivo working example showing that any agent as claimed could treat any diseases by inhibiting secretion of any non-neuronal inflammatory cell. It is unpredictable which undisclosed agent is effective for treating which disorder. Until the structure of agent is enabled, the specification merely extends an invitation to one of skilled in the art to further experiment to arrive at the claimed invention.

6. Claims 1-3, 8-9, 22-28, 38 and 40-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* or *all* "agent comprising at least any first and second domains" wherein the first domain cleaves any one or more proteins essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (2) *all* "agent comprising at least any first and second domains" wherein the first domain cleaves any one or more proteins essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell or for treating any disease, any disease such as the ones recited in claim 9, (3) *any* "agent comprising at least any first and second domains" further comprises any third domain for targeting the agent to said non-neuronal inflammatory cell for the claimed method, (4) a*ny* "agent comprising at least any first and second domains" further comprises any third domain wherein the third domain is IL-8 for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (5) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25,

synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell, (6) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell wherein the first domain comprises any light chain of a clostridial neurotoxin, any fragment of any light chain of a clostridial neurotoxin, any variant or derivative of any light chain of a clostridial neurotoxin, (7) *any* "agent comprising at least any first and second domains" wherein the first domain cleaves a protein selected form the SNAP-25, synaptobrevin and syntaxin essential to exocytosis and the second domain translocates said first domain into inflammatory cell for the claimed method of inhibiting secretion from any non-neuronal inflammatory cell wherein the second domain comprises any H_N region of a clostridial polypeptide, any fragment of any H_N region of a clostridial polypeptide, any variant or any derivative of any H_N region of a clostridial polypeptide that translocates the exocytosis inhibiting activity of the first domain into the inflammatory cell for the claimed method, (8) *any* agent comprising at least any first, second and third domains, wherein the first domain cleaves any one or more proteins essential to exocytosis, any second domain translocates the first domain into the cell and the third domain that binds to any non-neuronal inflammatory cell, (9) *any* pharmaceutical composition comprising any agent comprising at least any first, second and third domains, wherein the first domain cleaves any one or more proteins essential to exocytosis, any second domain translocates the first domain into the cell and the third domain that binds to any non-neuronal inflammatory cell in combination with a pharmaceutical acceptable carrier and (10) a method of treating any disease caused, exacerbated or maintained by secretion from any non-neuronal inflammatory cell using *any* "agent" mentioned above without the amino acid sequence.

The specification discloses only a polypeptide comprising a first domain, a second domain and a third domain wherein the first domain is a light chain of botulinum neurotoxin containing endopeptidase activity specific for a protein selected from the group consisting of SNAP-25, synaptobrevin and syntaxin covalently linked to a second domain wherein the second domain is a clostrial toxin heavy chain H_N that that translocates the first domain into the cytoplasm of a non-neuronal inflammatory cell and covalently linked to a third domain wherein the domain is wheat germ agglutinin capable of binding to the surface of non-neuronal

inflammatory cell. The specification further discloses a method of inhibiting secretion of histamine from human umbilical vein endothelial cells in vitro stimulated with von Willebrands factor using the polypeptide mentioned above in the presence low pH (page 42).

With the exception of the specific polypeptide mentioned above for inhibiting secretion in vitro, there is insufficient written description about the structure associated with function of all agent for inhibiting secretion form all non-neuronal inflammatory cell, much less for treating all disease such as the ones recited in claim 9.

The specification discloses only one polypeptide comprising botulinum neurotoxin BoNT containing endopeptidase activity fused to clostrial toxin heavy chain H_N and WGA, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of agent to describe the genus for the claimed method, the claimed agent and pharmaceutical composition comprising all agent. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 6/15/05 have been fully considered but are not found persuasive.

Applicants' position is that the specification describes on page 9, lines 1-30, the first domain comprises any polypeptide that cleaves one or more proteins essential to exocytosis (see lines 7-12 on page 8 of the specification). In more detail, the first domain is an endopeptidase polypeptide that cleaves an exocytosis protein selected from SNAP-25, synaptobrevin/VAMP and syntaxin.

In response to argument on pages 10-13, the claimed method encompasses a method of inhibiting secretion of non-inflammatory cell by administering any agent comprising at least any first, second and third domains. Claims 1 and 22 do not recite the specific agent comprising the specific first domain, and the specific second domain. Claim 23 does not recite the particular "fragment", "variant" or "derivative" of the light chain of clostridial neurotoxin. Claim 38 recites a method of treating any disease caused, exacerbated or maintained by secretion from any non-neuronal cell by administering to any patient any polypeptide that cleaves any one or more proteins essential to exocytosis.

In contrast to applicants' assertion that it would be apparent to a skilled person reading the present specification that any molecule having the desired function as recited in the claims would be suitable for use in an agent of the present invention, the agent or fusion protein comprising any first domain such as any "fragment", any "variant" or any "derivative" of any first domain and any "fragment", any "variant" or any "derivative" of the light chain of clostridial neurotoxin without the amino acid sequence has no structure, much less function. Likewise, the same reasoning applies to "second domain" such as "fragment", "variant" or "derivative" of the heavy chain of "H_N region of clostridial polypeptide", "polypeptide" in claim 38 and the "third domain" recited in claims 26, and 43-44. Further, the term "comprising" is opened ended. It expands the "first domain", the "fragment of light chain", "second domain" such as "H_N region of clostridial polypeptide", "fragment", "variant" or "derivative" of the heavy chain of "H_N region of clostridial polypeptide" to include additional amino acids at either or both ends. There is a lack of written description about which amino acids to be added, which amino acids to be deleted, which amino acids to be substituted for which amino acids such that the first and second domains maintain its structure and function, in turn, would be useful for the claimed method.

Given the unlimited number of agent or polypeptide and without the structure, i.e., amino acid sequence associated with function, the specification merely asks one of skilled in the art to come up with structure of an agent or polypeptide for the claimed method. Given the unlimited number of proteins on numerous non-neuronal inflammatory cells, the targeting third domain in the agent is not adequately described.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 9, 22-24, 26-28, and 40-45 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/07864 (Feb 26, 1998; PTO 1449).

The WO 98/07864 publication teaches an agent such as a polypeptide comprising a first, second and third domains wherein the first domain is clostridial toxin light chain, fragment and variant or derivatives thereof that cleaves one or more proteins essential to exocytotosis (see page 3, last paragraph, page 6, first paragraph, page 13, in particular), linked to a second domain such as H_N of clostridial toxin heavy chain, fragment, variants and derivatives thereof that translocates

the polypeptide into a target cell (see abstract, page 3, last paragraph, page 7, third paragraph, page 13-14, in particular) and a third domain such as Insulin-like growth factor-1 (IGF-1) that targets and binds to a specific cells such as insulin secreting cells (islet cell or endocrine cell), which is non-neuronal cell that involves in pancreatitis or inflammation of the pancreas (see abstract, page 8, first paragraph, in particular). The term "comprising" in claim 1 is open-ended. It expands the claimed agent to include a third domain of the reference polypeptide. The WO 98/07864 publication further teaches a pharmaceutical composition comprising the reference polypeptide and a pharmaceutically acceptable carrier (see claim 39 of WO 98/07864, in particular). The WO 98/07864 publication teaches a method of inhibiting secretion from non-neuronal cell using the reference polypeptide. The reference cleaves one or more vesicle or plasma membrane associated proteins such as SNAP-25, synaptobrevin/VAMP and syntaxin (see page 5, third full paragraph, in particular) that are essential to the specific cellular process of exocytosis and cleavage of these proteins results in inhibition of exocytoxis in non-neuronal cells, eukaryotic cells, insulin secreting cells (see page 4, third paragraph, in particular). Claim 45 is included in this rejection because the claimed method use the same agent for the same inflammatory cell population as taught by the WO98/07864 would inherently be able to treat inflammation associated with seasonal allergic rhinitis, allergic conjunctivitis, vasomotor rhinitis and food allergy. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 6/15/05 have been fully considered but are not found persuasive.

Applicants' position is that claim 26 recites that the third domain (and hence, the "agent" does not substantially bind to neuronal cells. Thus, the WO 98/07864 fails to disclose any method of inhibiting secretion from a non-neuronal inflammatory cell.

The amendment to claim 26 does not overcome this rejection because the WO 98/07864 publication teaches a method of inhibiting secretion from non-neuronal cell using the reference polypeptide. The reference cleaves one or more vesicle or plasma membrane associated proteins such as SNAP-25, synaptobrevin/VAMP and syntaxin (see page 5, third full paragraph, in particular) that are essential to the specific cellular process of exocytosis and cleavage of these proteins results in inhibition of exocytoxis in non-neuronal cells, eukaryotic cells, insulin secreting cells (see page 4, third paragraph, in particular). The insulin secreting cell taught in the WO 98/07864 is an endocrine cell that involves in inflammation. Further, the term " wherein said third domain does not substantially bind to neuronal cell" is irrelevant since the specification

does not define the term "does not substantially bind". The examiner interprets the term "not substantially binds" to mean it stills binds but to a lesser degree.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 3 and 8 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/07864 (Feb 26, 1998; PTO 1449) in view of WO 96/33273 (Oct 24, 1996; PTO 892) and Van Damme et al (Eur J Immunol 20(9): 2113-8, Sept 1990; PTO 892).

The teachings of the WO 98/07864 publication have been discussed supra.

The invention in claim 8 differs from the teachings of the references only in that the method wherein the third domain is IL8.

The WO 96/33273 publication teaches a method of targeting clostridial toxin to the cell of interest to inhibit secretion from neuronal inflammatory cell comprising administering an agent such as clostridial toxin light chain or fragment thereof that contains the protease activity (see claims 1-3 of WO 96/33273 publication, page 12-13, in particular), a second domain such as H_N of clostridial toxin heavy chain that translocates or internalizes the clostridial toxin light chain into a target cell (see page 13, 1st paragraph, claim 2 of WO 96/33273, in particular) and a targeting moiety (TM) such as inflammatory cytokine such as IL-8 that targets neutrophils (see page 13, 2nd paragraph, Table 1 on pages 24-25, in particular). The WO 96/33273 publication teaches that coupling of clostridial toxin to a new targeting function (the TM) give a novel agent

with new biological properties distinct from the native clostridial neural toxin (see page 15, last paragraph, in particular).

Van Damme et al teach IL8 secretion is associated with neutrophil activation during inflammatory reactions (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Insulin-like growth factor-1 (IGF-1) that targets and binds to an insulin secreting cells as taught by WO 98/07864 publication for the IL-8 as taught by the WO 96/33273 publication that binds to the neutrophils as taught by Van Damme et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Van Damme et al teach IL8 secretion is associated with neutrophil activation during inflammatory reactions (see abstract, in particular). The WO 96/33273 publication teaches that coupling of clostridial toxin to a new targeting function (the TM) give a novel agent with new biological properties distinct from the native clostridial neural toxin (see page 15, last paragraph, in particular). The WO 98/07864 publication teaches cleavage of one or more vesicle or plasma membrane associated proteins such as SNAP-25, synaptobrevin/VAMP and syntaxin by native clostridial neural toxin results in inhibition of secretion or exocytoxis in non-neuronal cells, eukaryotic cells, insulin secreting cells (see page 5, third full paragraph, page 4, third paragraph, in particular).

Applicants' arguments filed 6/15/05 have been fully considered but are not found persuasive.

Applicants' position is that a skilled person seeking to modify the agent of WO 98/07864 in order to create an agent that inhibits secretion from a non-neuronal cell would not turn to WO96/33273 which relates solely to targeting neuronal cell. One of skill in the art would not combine WO96/33273 with Van Damme et al. WO 96/33273 relates solely to targeting BoNT activity to neuronal cells whereas Van Damme et al is directed toward neutrophils, which are non-neuronal cells. There is no suggestion in WO 93/33273 that BoNT would have any activity in non-neuronal cells. The present invention is also not obvious over a combination of WO 98/07864 with Van Damme. In particular, the WO 98/07864 agents all have third domains that bind to neuronal cells (e.g. IGF-1) and hence WO 98/07864 targets to non-neuronal cells. Van Damme relates to non-neuronal cells (neutrophils) and hence a skilled person would not combine

the teachings of these two documents. Further, Van Damme et al further characterizing the role of IL-8 in neutrophils. Even if WO98/07864 and/or WO96/33273 were combined with Van Damme et al, this combination would fail to suggest the presently claimed invention. Van Damm et al teach away from using IL-8 as a third domain in an agent according to the present invention. Specifically, Van Damme et al describes the pro-inflammatory effects of IL-8 (see the 2nd sentence of the introduction, and first sentence of the discussion). In this regard, IL-8 is a potent inflammatory cytokine having chemoattractant properties for granulocytes. The binding of IL-8 to inflammatory cells induces an inflammatory response. IL-8 was initially identified due to its neutrophils activating and chemoattractant properties and increased IL-8 expression is seen in allergic inflammation. Thus a skilled person reading Van Damme would seek to inhibit IL-8 biding to target cells and would not consider IL-8 to be a suitable targeting moiety for anti-inflammatory agent of the present invention.

In response, the teachings of WO 98/07864 publication pertaining to an agent such as a polypeptide comprising a first, second and third domains wherein the first domain is clostridial toxin light chain, fragment and variant or derivatives thereof that cleaves one or more proteins essential to exocytotosis linked to a second domain such as H_N of clostridial toxin heavy chain, fragment, variants and derivatives thereof that translocate the polypeptide into a target cell and a third targeting domain such as Insulin-like growth factor-1 (IGF-1) that targets and binds to a specific cells such as insulin secreting cells (islet cell or endocrine cell), which is non-neuronal cell that involves in pancreatitis or inflammation of the pancreas (see abstract, page 8, first paragraph, in particular), the teachings of WO 96/33273 publication indicating the success in targeting inflammatory cell using IL-8 as a targeting domain that targets clostridial toxin to the to inhibit secretion from inflammatory neuronal cell instead of inflammatory non-neuronal cell and the teachings of Van Damme et al to IL8 secretion associated with non-neuronal inflammatory cells such as neutrophil having to target the agent to the inflammatory cell would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144. It is within the purview of one ordinary skilled in the art to substitute the targeting moiety such as IGF in the agent as taught by WO 98/07864 publication for the targeting

moiety such as IL-8 as taught by the WO 96/33273 publication that binds to inflammatory cells such as the neutrophils (non-neuronal) as taught by Van Damme et al or inflammatory pancreatic cell (neuroendocrine cell) as taught by WO 96/33273.

12. The following new ground of rejection is necessitated by the amendment filed 6/15/05.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 26-28, and 43-44 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The phrase "*does not substantially bind* to neuronal cell" in Claims 26, 43 and 44 represents a departure from the specification and the claims as originally filed. It would be helpful applicants point out the support for said phrase.

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
September 2, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600